Secondary prevention: improving outcomes following myocardial infarction

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In the first five years of the 1990s, the role of angiotensin converting enzyme (ACE) inhibitors in the treatment of patients with myocardial infarction was investigated in a series of large controlled trials involving more than 100 000 patients (table 1).[1]

The early use of ACE inhibitors after acute myocardial infarction (MI) has been investigated in four trials (CONSENSUS II, GISSI 3, ISIS 4, and CCS 1) involving more than 98 000 patients with treatment initiated within 24–36 hours from the onset of MI symptoms.[2–5]

Five of the trials (SAVE, AIRE, TRACE, and SOLVD prevention and treatment trials) involving a total of over 11 000 patients investigated the effects of late treatment with ACE inhibitors in patients with left ventricular dysfunction or failure.[6–10]

Early unselected trials

An overview of the early, unselected trials showed that 30 days after MI, patients allocated to ACE inhibitors had a significant reduction in mortality from 7.6% to 7.1% (p = 0.004), which corresponds to five lives saved per 1000 patients treated.[1 11]

In addition, there was a significantly lower rate of non-fatal congestive heart failure episodes, with a reduction from 15.2% among patients allocated to control, to 14.6% among patients allocated to ACE inhibitors (p = 0.01). This corresponds to the prevention of six cases of non-fatal heart failure per 1000 patients treated.[1 11]

Unexpectedly, the benefit of ACE inhibitors was achieved very early after the start of treatment; 239 fewer deaths were observed during the first 30 days in the group receiving ACE inhibitors than among those patients allocated to control. Of these 239 deaths, 200 were saved in the first week after the beginning of treatment and the onset of symptoms. This means that more than 80% of the benefit achieved with this strategy was achieved in the first week after the onset of MI symptoms.[1]

Long term follow up data from the GISSI-3 trial show that the early benefit of ACE inhibitors was maintained over a long period of time.

The benefits achieved after six weeks were still present four years later: eight lives saved per thousand at six weeks, five lives saved per thousand at six months, and nine lives saved per thousand at four years.[12]

Late selected trials

There were three key studies looking at the use of ACE inhibitors some days after MI in patients with left ventricular dysfunction or heart failure: SAVE, AIRE, and TRACE.[6–8]

The SAVE trial randomised more than 2000 patients with an ejection fraction < 40% to captopril or placebo.[6] The AIRE trial selected patients on the basis of clinical heart failure and approximately 2000 patients were randomised to ramipril or placebo.[7] And finally, the TRACE trial randomised patients to trandolapril or placebo if an echocardiographic evaluation of wall motion corresponded to an ejection fraction of ⩽ 35%.[8]

A recent overview of these trials showed that mortality was significantly reduced from 26.5% to 22.1% (p = 0.00001) in patients receiving ACE inhibitors. In absolute terms this corresponds to 44 lives saved per 1000 patients treated, which is highly significant. Similarly, the risk of reinfarction was reduced from 12.2% to 10.2% (p = 0.0004), corresponding to 20 reinfarctions prevented per 1000 patients treated.[1]

Clinical implications

WHEN TO TREAT?

There is no evidence of a time related benefit of ACE inhibitors. However, mechanistic studies have shown that early treatment reduces infarct expansion and ventricular enlargement. In addition, a review of the early trials shows that more than 80% of the total benefit of ACE inhibitors is achieved in the first week after the onset of symptoms[1 11] (fig 1). The benefit achieved in the first few days after acute MI is maintained over at least four years[12] (fig 2). It is therefore important not to miss the opportunity to save lives because of unnecessary delays.

WHO TO TREAT?

The overview of the early, unselected trials shows that the mortality reduction was similar among all the subgroups in the studies. In terms of adverse reactions, the risk of hypotension and renal dysfunction was similar in patients at different levels of risk, except in older patients (⩾ 75 years).[11]

With the exception of elderly patients, predictors of an increased risk of death such as prior MI, diabetes, anterior MI location, and

Table 1   Trials with ACE inhibitors in patients with acute myocardial infarction. Over five years, more than 100 000 patients with acute MI were randomised to ACE inhibitors

Four early unselected trials		Five late selected trials	
CONSENSUS-2	6090	SAVE	2231
GISSI-3	19394	AIRE	1986
ISIS-4	58050	TRACE	1749
CCS-1	14962	SOLVD-P	3382
		SOLVD-T	1687
Subtotal	98496	Subtotal	11035
	Total	109531	

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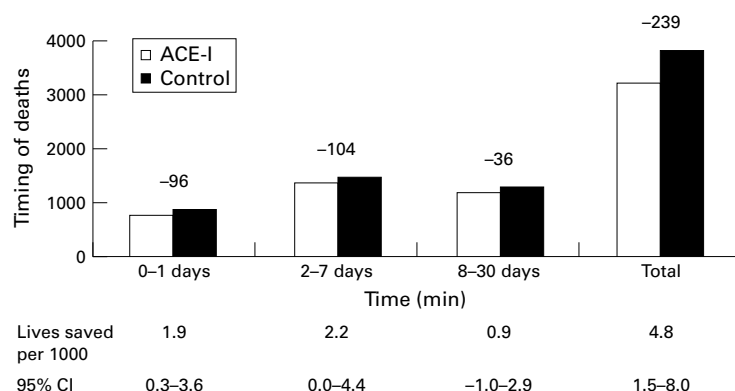Dr Maggioni
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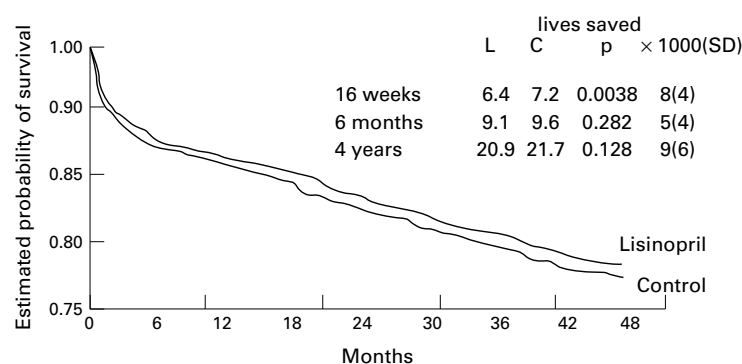*Figure 1   Timing of deaths in first 30 days following treatment.*

Figure 2   Estimated probability of survival up to four years following lisinopril or placebo treatment.

elevated heart rate, or a Killip class > 1, were associated with greater benefits of ACE inhibitor treatment.[1][11]

CLINICAL RECOMMENDATIONS

ACE inhibitors should be considered in every MI patient with a systolic blood pressure higher than 100 mm Hg, provided there is no clear contraindication, soon after the administration of other recommended treatments, such as β blockers, aspirin, and reperfusion therapy. Patients at increased risk of death receive a greater absolute benefit from early ACE inhibitor treatment.[1] Elderly patients (over 75 years) are at increased risk of hypotension and there is no evidence in the overview of a survival advantage in this group.

All these patients should be re-evaluated at discharge, or after two weeks. ACE inhibitor treatment should be continued long term only in those patients with overt heart failure or extensive left ventricular dysfunction.[1]

COST OF TREATMENT

The cost of this strategy is reasonable. A pharmacoeconomic analysis of the GISSI-3 trial shows that using lisinopril in patients after MI (early treatment) costs approximately $2200 per life saved.[13] Treating patients with left ventricular dysfunction for four years following discharge costs approximately $10 000 per year or life saved.[11]

CURRENT CLINICAL PRACTICE

A survey in the first three months of 1999 among Italian patients looked at how evidence based recommendations translate into clinical practice. The study showed that ACE inhibitors for the treatment of myocardial infarction in the acute phase (< 24 hours) are clearly underused with an actual use of only 39% compared with an expected use of 70% (Latin Survey presented at the Cardiac Emergency Strategies for Y2K, Rome, Italy, October 15, 1999).

With respect to the secondary prevention strategies, ACE inhibitors are recommended in 38% of patients with left ventricular dysfunction. The rate of use of this drug was more than expected with 57% actual use.[14]

HOPE STUDY

Until recently there were no definitive data with respect to the effect of ACE inhibitors in post-MI patients without heart failure and with preserved left ventricular function. However, at the 21st congress of the European Society of Cardiology in 1999, important new data from the HOPE study on the use of ACE inhibitors in patients at high risk of cardiovascular events were presented for the first time.[15]

The HOPE study was a large scale, four year, randomised, double blind, placebo controlled study to evaluate ramipril and vitamin E in 9541 patients. Patients at high risk of developing a major cardiovascular event were included, defined as those with a history of vascular disease, or with diabetes plus one other coronary risk factor. Patients were excluded if they had heart failure or a low ejection fraction, were already taking an ACE inhibitor or vitamin E, or had an acute event in the previous four weeks.

There was a significant reduction of the composite end point of MI, stroke, and cardiovascular death from 17.5% among patients randomised to placebo, to 13.9% among those randomised to ACE inhibitors. The reduction is approximately 22% and is highly significant (p = 0.000002). This benefit is also seen in all the subgroups of patients.

Importantly, these results were obtained on top of the other recommended treatments. At the beginning of the trial, about 75% of patients were treated with antiplatelets; lipid lowering was used in 29% of patients; β blockers were used in 39%; diuretics in 15%; and calcium channel blockers in 47%.

There is overwhelming evidence from HOPE that ACE inhibitors prevent cardiovascular deaths, stroke, MI, and heart failure, and reduce the rate of hospital admission for revascularisation. There is the interesting observation that in non-diabetic patients allocated to ramipril, there was a reduced rate of diabetes development in comparison with placebo. Moreover, diabetic microvascular complications were significantly reduced in the ACE inhibitor group. These benefits are consistently observed in a very broad range of high risk patients and in addition to other effective treatments. The only adverse event was cough, which was observed in 5% more patients in the ACE inhibitor group than in the placebo group.

Trial acronyms
AIRE: Acute Infarction Ramipril Efficacy
CCS 1: Chinese Cardiac Study 1
CONSENSUS II: Co-operative North Scandinavian Enalapril Survival Study
EUROPA: European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease
GISSI 3: Gruppos Italiano per lo Studio Sella sopravvivenza nell'Infarcto miocardico
HOPE: Heart Outcomes Prevention Evaluation
ISIS 4: Fourth International Study of Infarct Survival
PEACE: Prevention of Events with Angiotensin-Converting Enzyme inhibition
SAVE: Survival and Ventricular Enlargement
SOLVD: Studies of Left Ventricular Dysfunction
TRACE: Trandolapril Cardiac Evaluation

Ongoing trials

HOPE is not the only trial testing the hypothesis of treating coronary patients without left ventricular dysfunction or heart failure. There are at least two further ongoing trials testing this hypothesis in patients at lower risk than those randomised in HOPE: PEACE and EUROPA.[16 17]

The PEACE trial is recruiting over 8000 patients and is comparing trandolapril with placebo.[14] All patients have well documented coronary heart disease and an ejection fraction higher than 40%. The primary end point is MI, cardiovascular death, and the rate of revascularisation procedures. The follow up is 5.5 years.

The EUROPA trial is looking at perindopril versus placebo in more than 10 000 patients.[15] All patients have well documented coronary artery disease. End points include death and MI. The follow up is 3.75 years.

Conclusion

Long term ACE inhibitor treatment is strongly recommended in patients with documented coronary artery disease and when these patients show clinical signs or symptoms of heart failure and left ventricular dysfunction. The HOPE trial supported the indication of long term ACE inhibitor treatment of all patients at high risk of cardiovascular events. However, at least one of the two ongoing trials, PEACE and EUROPA, should be completed before a definite conclusion about the use of ACE inhibitors for all patients with coronary artery disease, or who are at high risk, is reached.

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